

Tumor Lysis Syndrome in Patients with Light Chain Multiple Myeloma: Report of Two Cases

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Tumor lysis syndrome (TLS) is a severe life-threatening complication which typically occurs in highly proliferative malignancies, such as Burkitt's lymphoma, acute leukemia or germ cell tumors. Although TLS is unusual in multiple myeloma, it should not be overlooked as it is associated with significant morbidity. In recent years, emerging new agents such as thalidomide and bortezomib have been found to be highly effective in the treatment of multiple myeloma. In this milieu, there is greater concern that the rate of TLS in multiple myeloma will increase. We herein report 2 patients with light chain multiple myeloma who developed TLS during treatment. One patient improved after hydration, allopurinol and forced diuresis. The other underwent hemodialysis because of oliguria. These 2 patients did not have heavy tumor burdens. They also lacked risk factors of TLS that were described in previous reports. Our experience suggests light chain myeloma with underlying myeloma kidney is associated with a risk of TLS. Clinical awareness, close monitoring and early intervention are the keystones in the management of these patients. (*Chang Gung Med J* 2011;34(6 Suppl):70-5)

Key words: tumor lysis syndrome, multiple myeloma, immunoglobulin light chain, renal insufficiency

Tumor lysis syndrome (TLS) is a serious, life-threatening complication in the treatment of neoplasms. It has been reported, although infrequently, among patients with multiple myeloma. Some risk factors for myeloma patients, such as hyperproliferative diseases, immature plasma cell morphology, circulating plasmablasts, unfavorable cytogenetics, and increased lactate dehydrogenase (LDH), have been identified. Multiple myeloma of the light chain isotype is frequently associated with myeloma kidney and renal dysfunction. This impairment of kidney function, however, has never been reported to play a role in the development of TLS. In recent years, emerging new therapeutic agents have brought multiple myeloma to a new era. Both thalidomide and bortezomib-based regimens have been shown to

improve treatment responses and overall outcomes. Both thalidomide and bortezomib, however, have been reported to cause TLS. It is possible, therefore, that TLS will be an emerging complication in this new era of myeloma treatment. We describe two patients with light chain multiple myeloma who developed TLS shortly after the first treatment. Our experience suggests light chain disease is a possible risk factor for the development of TLS.

CASE REPORT

Case 1

A 44 year-old man presented with a 3-week history of bilateral lower leg pain and paresthesia. A physical examination showed unremarkable findings.

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Magnetic resonance imaging revealed multiple lesions in the cervical, thoracic and lumbar spine causing spinal cord compression in the T7-9 segments. A biopsy revealed plasmacytoma. Extensive skeletal radiography revealed no osteolytic lesions. Local irradiation to the spine was administered. A bone marrow aspiration smear showed plasma cells accounting for 22% of all nucleated cells. No plasmablasts were observed. Serum and urine protein immunofixation revealed lambda light M-protein.

The patient had a normal hemogram (hemoglobin 13 g/dL, white blood cells 9100/ μ L, and platelets 255,000/ μ L). The pretreatment biochemical profile revealed blood urea nitrogen (BUN) 43 mg/dL, creatinine 2.37 mg/dL, Na 136 mEq/L, K 5.3 mEq/L, calcium 9.6 mg/dL, phosphate 5.3 mg/dL, LDH 132 IU/L and uric acid 7.7 mg/dL. Serum immunoglobulin levels were IgG 625 mg/dL, IgA 118 mg/dL, IgM 24.5 mg/dL. While receiving radiotherapy to the spine, he was given treatment with thalidomide 100 mg and dexamethasone 40 mg per day. At the same time, he received intravenous hydration of more than 3 liters a day. His appetite and intake were fair. No immediate side effects except for insomnia during treatment. Four days after initiating treatment, laboratory data showed BUN 69 mg/dL, creatinine 3.22 mg/dL, Na 127 mEq/L, K 6.9 mEq/L, calcium 9.1 mg/dL, phosphate 6.9 mg/dL and uric acid 8.4 mg/dL. Under the impression of tumor lysis syndrome, the patient was given a glucose and insulin infusion for hyperkalemia, further hydration, forced diuresis with furosemide, allopurinol and calcium polystyrene sulfonate. The data showed creatinine 3.22 mg/dL, Na 128 mEq/L, K 5.2 mEq/L, and uric acid 9.1 mg/dL after 24 hours' treatment and BUN 43 mg/dL, creatinine 2.51 mg/dL, Na 131 mEq/L, K 3.9 mEq/L, calcium 8.2 mg/dL, phosphate 4.3 mg/dL and uric acid 6.7 mg/dL after 48 hours. The laboratory parameters of this patient are summarized in Fig. 1A. The patient underwent further treatment courses with thalidomide and dexamethasone without TLS. He subsequently received autologous stem cell transplantation and remained in remission as of the writing of this article.

Case 2

A 58-year-old woman was found to have renal insufficiency in a health examination six months before admission. She reported no bone pain or

dizziness but had a gradual onset of fatigue and anorexia. On admission, physical examination showed unremarkable findings. The biochemistry profile revealed BUN 32 mg/dL, creatinine 4.05 mg/dL, Na 138 mEq/L, K 4.3 mEq/L, calcium 9.3 mg/dL, phosphate 4.3 mg/dL, LDH 177 IU/L and uric acid 7.2 mg/dL. Serum levels of immunoglobulins were IgG 13.60 mg/dL, IgA 186 mg/dL, and IgM 74.3 mg/dL. Serum and urine protein immunofixation revealed the presence of lambda light chain M-protein. Extensive skeletal radiography revealed no osteolytic lesions. A bone marrow aspiration smear showed plasma cells accounting for 39% of all nucleated cells. No plasmablasts were observed. The diagnosis of multiple myeloma was established. The patient received chemotherapy with vincristine, adriamycin and dexamethasone. She was treated with hydration and urine alkalinization. She developed mild anorexia. On the third day of chemotherapy, the biochemical data showed BUN 88 mg/dL, creatinine 8.8 mg/dL, Na 115 mEq/L, K 4.9 mEq/L, calcium 7.5 mg/dL, phosphate 9.4 mg/dL, and uric acid 8.8 mg/dL. Under the impression of tumor lysis syndrome, she was given careful hydration, allopurinol and furosemide. Despite medical treatment, she developed oliguria and hemodialysis was initiated on the fifth day of chemotherapy. After 2 sessions of hemodialysis, the laboratory data were BUN 60 mg/dL, creatinine 8.03 mg/dL, Na 126 mEq/L, K 3.5 mEq/L, calcium 7.2 mg/dL, phosphate 6.5 mg/dL, and uric acid 5.6 mg/dL. She continued to receive dialysis regularly because of sustained oliguria. Subsequent data are summarized in Fig. 1B. She was transferred to another hospital for maintenance dialysis at the patient's convenience.

DISCUSSION

This report raises clinical awareness of TLS in patients with multiple myeloma, especially the light chain isotype with pre-existing renal insufficiency.

TLS is a constellation of metabolic and electrolyte abnormalities including hyperkalemia, hyperuricemia, hyperphosphatemia and renal function impairment.⁽¹⁾ It usually develops in patients with highly proliferative hematological malignancies such as leukemia and high grade lymphoma. Compared with acute leukemia and high grade lymphoma, multiple myeloma is relatively indolent, and therefore

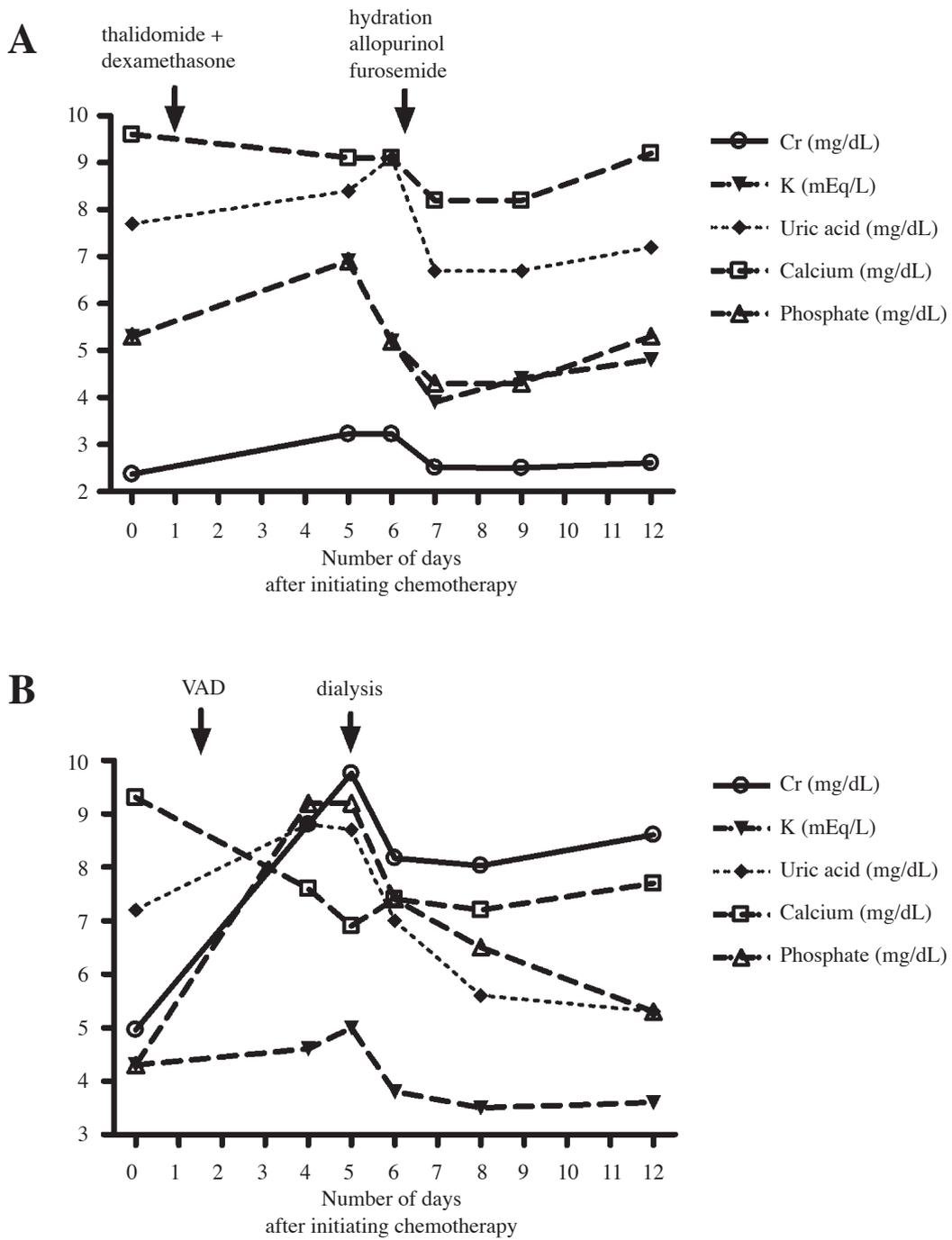


Figure Temporal changes in creatinine, electrolytes and uric acid concentrations in 2 patients with λ light chain multiple myeloma before, during and after the development of tumor lysis syndrome (TLS). (A) In case 1, TLS developed after combination treatment with thalidomide and dexamethasone. The parameters of TLS improved after treatment with hydration, allopurinol and diuresis. (B) In case 2, TLS developed after chemotherapy with vincristine, adriamycin and dexamethasone. Hemodialysis was initiated because of oliguria. The creatinine levels remained high despite improvement of uric acid and other parameters.

less commonly associated with TLS.⁽²⁾ However, there are scattered reports of TLS in multiple myeloma patients. In multiple myeloma, TLS may occur after various treatment modalities including monotherapy with bortezomib,⁽³⁻⁵⁾ steroids⁽⁶⁾ and thalidomide,^(7,8) raising concerns about TLS during myeloma treatment. In the largest series, Fassas et al reviewed 820 patients treated over 9 years in a single institution and identified 9 such cases (incidence 1.1%), including 6 cases with IgG, 2 with IgA and 1 with light chain isotype paraproteins.⁽²⁾ Although infrequently encountered, TLS in multiple myeloma should not be overlooked as it is associated with significant mortality and morbidity.

Some clinical features appear to be associated with the risk of myeloma patients developing TLS. In the case series of Fassas et al, all patients with TLS had extensive bone marrow plasmacytosis (plasma cells > 70% of all nucleated cells). Most patients had hyperproliferative diseases and immature plasma cell morphology (presence of plasmablasts, as defined by Greipp et al.).^(2,9) Other possible risk factors, including circulating plasmablasts, unfavorable cytogenetics, and increased LDH, have also been proposed.⁽¹⁰⁾

It is not uncommon for multiple myeloma patients to have compromised renal function. Multiple factors such as dehydration, infection, and hypercalcemia may contribute to renal insufficiency. TLS, therefore, should be differentiated from renal dysfunction resulting from other etiologies. The dynamic changes in related parameters, as in our cases, are the most reliable markers for diagnosis. Fassas et al. proposed diagnostic criteria based on such dynamic changes. Both cases in our report fulfilled the proposed diagnostic criteria for TLS.⁽²⁾ Compared with other reports of TLS in multiple myeloma patients, the 2 patients in the present report did not have any of the clinical risk factors reported to be associated with TLS in multiple myeloma. Plasma cells accounted for 22% and 39% respectively, suggesting relatively low myeloma cell burdens. The residual IgG, IgA and IgM were nearly normal in both cases. No plasmablasts or circulating plasma cells were observed. On the other hand, the striking characteristic of both cases was the impaired renal function before initiating treatment. Although not mentioned in reports of myeloma patients with TLS, renal dysfunction has been identified as a risk factor

for TLS in other hematologic malignancies.⁽¹¹⁾ Although the etiology of impaired kidney function in these patients is often multifactorial, myeloma kidney, which is characteristic of light chain isotype myeloma, possibly plays the most important role. Because the kidney is responsible for excretion of uric acid, phosphate and potassium,⁽¹⁾ it is likely that patients with myeloma kidneys are more susceptible to TLS. In fact, although renal insufficiency was not considered a risk factor for TLS in multiple myeloma, many myeloma-associated TLS cases reported in the literature were found to have renal function impairment. In the series reported by Fassas et al., 6 of 9 cases (67%) had pre-existing renal insufficiency. This series may also highlight the importance of light chain multiple myeloma for TLS, as the only patient who required hemodialysis also had light chain myeloma. Similarly, our experience with the 2 cases described in this article suggests that in patients with light chain myeloma, the tumor burden and proliferation index are not the main risk factors leading to TLS. In contrast, renal insufficiency with impaired function to maintain physiological homeostasis is likely to play the key role, although more studies and reports are needed to validate these theories.

Prevention and management of TLS in multiple myeloma is identical to that with other etiologies. The keystones to success are early recognition and adequate hydration,⁽¹¹⁾ as in our first case. Hemodialysis should be initiated in time to treat life-threatening metabolic and electrolyte disturbances,⁽¹¹⁾ as in our second case.

In conclusion, our experience with these 2 cases suggests TLS is a potentially severe adverse effect complicating myeloma treatment. Parameters related to TLS, including creatinine, uric acid, LDH, calcium, and phosphate, should be closely monitored after initiating treatment, as suggested in practice guidelines.⁽¹¹⁾

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輕鏈型多發性骨髓瘤發生腫瘤溶解症候群：兩例個案報告

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腫瘤溶解症候群 (Tumor lysis syndrome, TLS) 通常發生在高度增生性之惡性疾患，如白血病、高惡性度淋巴瘤、生殖細胞瘤，是一種嚴重且危及生命的併發症。雖然腫瘤溶解症候群不常發生於多發性骨髓瘤 (multiple myeloma)，它卻會顯著增加病患罹病嚴重程度，因此腫瘤溶解症候群應是一個臨床上不容忽視的問題。近年來，新興藥物如賽得 (thalidomide)、萬科 (bortezomib, velcade[®]) 的崛起讓多發性骨髓瘤的治療邁入了一個新時代，這些藥物的高效度也令人提高了對腫瘤溶解症候群發生的顧慮。本文報告兩位罹患輕鏈 (light chain) 型多發性骨髓瘤之病患在治療過程中發生腫瘤溶解症候群之個案。其中一位在給予大量水份、降尿酸藥物及利尿劑後病情改善，另一位因發生寡尿症狀而須接受血液透析治療。這兩位病患腫瘤負荷量並不很高，也沒有在文獻報告中易發生腫瘤溶解症候群的危險因子。我們這樣的臨床經驗顯示輕鏈型多發性骨髓瘤對腎臟常有影響，可能是腫瘤溶解症候群的危險因子之一。處置成功的關鍵則在於高度懷疑、密切監測及早期適切的介入治療。(長庚醫誌 2011;34(6 Suppl):70-5)

關鍵詞：腫瘤溶解症候群，多發性骨髓瘤，輕鏈免疫球蛋白，腎衰竭

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